MMP-3 deficiency suppresses endotoxin-induced acute inflammation in the eye

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Introduction: Matrix metalloproteinase-3 (MMP-3) is well known to mediate neuroinflammatory processes by activating microglia, disrupting blood-CNS barriers and supporting neutrophil influx into the brain. Also the posterior part of the eye, more specifically the retina, the retinal pigment epithelium (RPE) and the blood-retinal barrier (BRB), is affected upon neuroinflammation, but a role for MMP-3 during ocular inflammation remains elusive.

Materials and methods: To investigate whether MMP-3 contributes to acute inflammation in the eye, the endotoxin-induced uveitis (EIU) model was applied in mice via intraperitoneal administration of lipopolysaccharide (LPS) from Salmonella enterica, using wild-type and MMP-3 deficient (MMP-3$^{-/-}$) mice and the semi-specific MMP-3 inhibitor NNGH. The spatiotemporal expression pattern of MMP-3 during EIU was first evaluated using quantitative PCR (qPCR), Western blotting (WB) and immunohistochemistry. Optical coherence tomography (OCT) and the optokinetic tracking response were applied to study respectively general retinal morphology and visual acuity of healthy MMP-3$^{-/-}$ mice. Leukostasis and leukocyte infiltration were studied via respectively perfusion labelling with FITC-conjugated Concanavalin A lectin and OCT. qRT-PCR, a multiplex cytokine bead assay and WB were applied to investigate the expression level of inflammatory-associated molecules.

Results: Healthy MMP-3$^{-/-}$ mice did not show an aberrant retinal morphology or visual acuity. Systemic administration of LPS induced MMP-3 mRNA and protein expression in the posterior part of the eye, predominantly in the RPE. MMP-3 deficiency or knockdown attenuated the hypothermic response after endotoxemia, suppressed leukocyte adhesion to the retinal vasculature and leukocyte infiltration into the vitreous cavity in mice subjected to EIU. Moreover, mRNA levels of intercellular adhesion molecule 1 (*Icam1*), interleukin 6 (*Il6*) and cytokine-inducible nitrogen oxide synthase

(*Nos2*), which are key molecules involved in EIU, were clearly reduced in MMP-3$^{-/-}$ retinal and RPE samples. In addition, loss of MMP-3 repressed the protein levels of the chemokines monocyte chemoattractant protein (MCP)-1 and (C-X-C motif) ligand 1 (CXCL1).

Conclusion: These findings suggest an important contribution of MMP-3 to the inflammatory processes during EIU, and its potential use as a therapeutic drug target in reducing ocular inflammation.